Jikeikai Med J 2021 ; 68 : 99-109

Risk Factors of Moderate-to-severe Exacerbation in Patients with Chronic Obstructive Pulmonary Disease

Takanori NUMATA, Jun ARAYA, Yuma MATSUI, Keitaro OKUDA, Junko WATANABE, Naoko TAKAHASHI, Hanae MIYAGAWA, Yu FUJITA, Daisuke TAKEKOSHI, Hirofumi UTSUMI, Mitsuo HASHIMOTO, Saburo ITO, Hiroshi WAKUI, Shunsuke MINAGAWA, Hiromichi HARA, and Kazuyoshi KUWANO

Division of Respiratory Diseases, Department of Internal Medicine, The Jikei University School of Medicine

ABSTRACT

Objective : Exacerbations are linked to a poor prognosis of patients with chronic obstructive pulmonary disease (COPD). Eosinophilia is an important determinant of COPD phenotypes and is associated with a high frequency of exacerbation and the increased effectiveness of inhaled corticosteroids. We examined the clinical characteristics of patients with COPD exacerbations, including eosinophilia.

Methods : This was a single-center, retrospective study. A total of 138 patients with COPD from January 2018 through December 2019 were reviewed and evaluated on the basis of characteristics, biomarkers, pulmonary function, and the number of exacerbations.

Results : The analysis of 43 patients with moderate-to-severe exacerbations and 95 without exacerbations demonstrated that risk factors for moderate-to-severe exacerbations were the body mass index (odds ratio : 0.87, $p=0.017$) and the severity of COPD (odds ratio : 2.8, $p=0.032$). Furthermore, risk factors for severe exacerbations were greater age and a history of exacerbations. The frequency of inhaled corticosteroids use was significantly greater for patients with eosinophilic (eosinophil $\geq$ 300/μl or$\geq$5%) COPD (21 patients [33%]) than patients with noneosinophilic COPD (4 patients [5%], $p<0.0001$), but the number of moderate-to-severe exacerbations did not differ.

Conclusions : Risk factors for exacerbations in patients with COPD are greater age, lower body mass index, severe COPD, and a history of exacerbations. Treatment with inhaled corticosteroids might decrease the risk of exacerbation, especially in patients with eosinophilia.

(Jikeikai Med J 2021 ; 68 : 99-109)

Key words : chronic obstructive pulmonary disease, exacerbation, body mass index, eosinophil, inhaled corticosteroid, pneumonia

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitations and respiratory symptoms, such as cough and dyspnea. Exposure to noxious particles or gases, including cigarette smoke, is the main cause of COPD[1]. The mortality rate of patients with COPD is increasing worldwide[1]. Although the prevalence of COPD in

Received : November 2, 2021 / Accepted : December 15, 2021
沼田 尊功, 荒屋 潤, 松井 勇磨, 奥田慶太郎, 渡部 淳子, 高橋 直子, 宮川 英恵, 藤田 雄, 竹越 大輔, 内海 裕文, 橋本 典生, 伊藤 三郎, 和久井 大, 皆川 俊介, 原 弘道, 桑野 和善

Mailing address : Takanori Numata, Division of Respiratory Diseases, Department of Internal Medicine, The Jikei University School of Medicine, 3-25-8, Nishi-Shimbashi, Minato-ku, Tokyo, 105-8461, Japan

E-mail : t-numata@jikei.ac.jp

Japan in 2000 was 8.6%, only a small proportion of patients were treated for COPD[2]. Furthermore, the airflow limitation is progressive and cannot be completely reversed by treatment with the available bronchodilators[1].

Based on the definition of the Global Initiative for Chronic Obstructive Lung Disease (GOLD), the exacerbation of COPD is represented by a worsening of respiratory symptoms and leads to a change in medication. The exacerbation of COPD is an important prognostic factor, and severe exacerbation has been reported to increase the mortality rate[3]. Exacerbation has been shown with cluster analysis to be classified into 4 different phenotypes : bacterial-predominant, viral-predominant, eosinophil-predominant, and pauci-inflammatory[4]. These phenotypes of COPD exacerbation have been suggested to affect the efficacy of treatment.

The standard treatment of COPD is the inhalation of long-acting bronchodilators containing long-acting β_2 agonists and long-acting muscarinic antagonists[1,5]. The 2020 GOLD report suggested categories that could be used to guide therapeutic decision-making based on the symptoms and the number of exacerbations or hospitalizations[1]. Several randomized controlled trials have reported the efficacy of additional inhaled corticosteroids with regard to reducing exacerbations, which are sometimes associated with the peripheral blood eosinophil (PBE) count[6,7]. Accordingly, the GOLD report recommends the use of not only long-acting bronchodilators but also additional inhaled corticosteroids for patients with symptomatic COPD and frequent exacerbations, especially those with eosinophilia ($\geq$300/μl)[1]. However, the efficacy of inhaled corticosteroids as a treatment of eosinophilic COPD and the association of treatment with inhaled corticosteroids and the number of COPD exacerbations in the real-world clinical setting remain unclear in Japan[8].

Accordingly, we performed the present single-center, retrospective study to determine the association between exacerbations and patient characteristics, including COPD phenotype and inhaled corticosteroid treatment.

METHODS

Study objective and design

The objective of the study was to determine the risk factors for exacerbation in terms of clinical characteristics, including the COPD phenotype. This study design is a single-center, retrospective study.

Patients

We examined patients who had COPD and had regularly attended The Jikei University Hospital for at least 12 months from January 2018 through December 2019. The COPD in all patients had been diagnosed by respiratory physicians on the basis of GOLD guideline 2017[9] and Japanese Respiratory Society guidelines regarding COPD[5]. Cases of COPD with an eosinophilic phenotype, referred to as "eosinophilic COPD" was defined as COPD with eosinophilia (PBE count $\geq$ 300/μl or percentage of eosinophils $\geq$ 5%)[10,11]. Laboratory data were collected during the period of stable disease status before the data cutoff (December 31, 2019).

An exacerbation of COPD was defined as worsening of the patient's symptoms of cough, sputum, or breathlessness requiring a change in medication. Exacerbations were classified as "moderate" if additional treatment with systemic corticosteroids or antibiotics or both was required and were classified as "severe" if hospitalization was required. Mild exacerbation required occasional use of short-acting β_2 agonists and was not included in the study. Because the incidence of exacerbations is lower in Japanese patients with COPD than in European patients and because the rate of complications with pneumonia is higher in Japan owing to the widespread use of computed tomographic imaging[12,13], patients with pneumonia were not excluded from the groups of patients with exacerbations.

The exclusion criteria were the patient visiting for less than 12 months and being hospitalized for reasons other than COPD exacerbations, such as a cardiac event, surgery, and the treatment of lung cancer. Also excluded were patients with asthma-COPD overlap[1]. Finally, 138 patients with COPD were reviewed and analyzed.

This study was approved by the Ethics Committee of The Jikei University School of Medicine for Biomedical Research (32-237 [10318]). Based on the ethics guidelines of The Jikei University, the need to obtain written informed consent was waived because of the retrospective design, and an opt-out consent statement was posted on the website of our hospital.

Data collection and evaluation

The following characteristics of each patient were reviewed : sex, age, smoking status, body mass index (BMI), and baseline treatments. The following variables

were examined when the patient's condition was stable : peripheral white blood cell count, PBE count, serum immunoglobulin E, pulmonary function test results (forced vital capacity [FVC], forced expiratory volume in 1 second [FEV_1], FEV_1/FVC, and the percentage of predicted FEV_1 [%FEV_1]), comorbid pneumonia, and the number of moderate-to-severe exacerbations in the past 5 years. All enrolled patients were evaluated with no distinction between those with persistent eosinophilia and those with intermittent eosinophilia. The number of annual exacerbations of COPD was defined as the total number of exacerbations $\times 12$/the total duration of the observation period (months). All patients who had been hospitalized had undergone blood tests and computed tomography of the chest. The primary goal was to identify risk factors for moderate-to-severe exacerbations. The secondary outcome was to identify the clinical characteristics of patients with eosinophilic phenotypes and the risk factors for pneumonia.

Statistical analyses

All statistical analyses were performed with the software program StatView version 5 (SAS Institute, Inc., Cary, NC, USA). All values are expressed as the means ± standard deviations. A p-value<0.05 was considered statistically significant. The factors associated with patient characteristics were examined with Mann-Whitney *U* tests, Fisher's exact tests, chi-square tests, or Wilcoxon signed-rank tests. Evaluations among multiple groups were performed with analysis of variance and Bonferroni post hoc correction. Univariate logistic regression was performed with the following variables, which were reported in previous studies as risk factors for exacerbations and pneumonia : sex (male), age, BMI, COPD severity (GOLD stage≥III), PBE count (≥300/μl), history of exacerbations, current inhaled corticosteroid use, and current dual use of bronchodilators (long-acting β_2 agonists/long-acting muscarinic antagonists). A multivariate logistic regression was then performed to evaluate the variables that achieved a value of $p<0.20$ in the univariate models.

Results

Patient characteristics and COPD exacerbation

Of the 138 patients with COPD, 43 had moderate-to-severe exacerbations in the previous year and 95 patients did not (Table 1). Patients with exacerbation in the previous year, compared with patients without, had significantly greater age (76.4 vs. 72.5 years, $p=0.01$), lower BMI (21.4 ± 3.4 vs. 24.0 ± 4.0 kg/m^2, p=0.0004), greater severity of COPD, and poorer pulmonary function (such as %FEV_1 : 57.1 ± 21.6 vs 71.3 ± 18.0 %, $p=0.0002$). The average number of moderate-to-severe exacerbations per year in the past 5 years (mean observation period, 45.4 months) was significantly greater in patients who had moderate-to-severe exacerbation in the previous year (1.08 ± 1.07/person-year) than in patients who did not (0.08 ± 0.19/person-year, $p<0.0001$). Furthermore, the mean number of moderate-to-severe exacerbations in the previous year was directly related to the severity of COPD (Fig. 1).

Risk factors for moderate-to-severe and severe exacerbation

Risk factors for moderate-to-severe exacerbations of COPD, as shown with univariate and multivariate logistic regression analysis (Table 2), were the BMI (odds ratio [OR], 0.87 ; 95% confidence interval [CI], 0.77-0.97 ; $p=0.017$] and COPD stages III and IV (OR, 2.8 ; 95% CI, 1.1-7.0 ; $p=0.032$). Furthermore, analysis with univariate and multivariate logistic regression models (Table 2) showed that the risk factors for severe exacerbations were greater age (OR, 1.11 ; 95% CI, 1.02-1.21 ; $p=0.013$) and a history of exacerbations (OR, 8.8 ; 95% CI, 2.2-34.4 ; $p=0.002$). In contrast, eosinophilia was not a significant risk factor for COPD exacerbations.

Comparison of patients with or without an eosinophilic phenotype

Of the 138 patients, 64 had the eosinophilic COPD phenotype and 74 had the noneosinophilic COPD phenotype (Table 3). The PBE count during a period of stable disease status without exacerbation and the percentage of patients being treated with inhaled corticosteroids were both significantly higher in patients with eosinophilic COPD than in patients with noneosinophilic COPD. Furthermore, the average number of annual moderate-to-severe exacerbations in the previous 5 years was higher, but not to a significant degree, in patients with eosinophilic COPD (0.47 ± 0.87) than in patients with noneosinophilic COPD (0.32 ± 0.67, $p=0.05$).

Of the 64 patients with eosinophilic COPD, 22 (34%) had an exacerbation in the previous year (Table 3). Signifi-

Table 1. Characteristics of patients with or without exacerbation of chronic obstructive pulmonary disease

Characteristic	All patients (n=138)	Moderate-to-severe exacerbation in previous year		p value
		Patients with (n=43)	Patients without (n=95)	
Male	120 (87)	36 (84)	84 (88)	0.63
Mean age (range), years	73.7 (50-92)	76.4 (63-92)	72.5 (50-89)	0.01
Body mass index, kg/m^2 (SD)	23.2 (4.0)	21.4 (3.4)	24.0 (4.0)	0.0004
Smoking, former / current	118 / 20	36 / 7	82 / 13	0.89
Smoking index, pack-year	62 (37)	62 (29)	62 (40)	0.46
Phenotypes eosinophilic or noneosinophilic				
Eosinophilic COPD	64 (46)	22 (51)	42 (44)	0.57
COPD stage I / II / III / IV	38 / 69 / 23 / 8	6 / 19 / 13 / 5	32 / 50 / 10 / 3	0.002
FVC, ml	3192 (834)	2812 (896)	3364 (748)	0.0003
%FVC	97.0 (20.8)	90.1 (23.1)	100.1 (19.0)	0.01
FEV_1, ml	1738 (636)	1384 (628)	1898 (575)	<0.0001
$\%FEV_1$	66.9 (20.2)	57.1 (21.6)	71.3 (18.0)	0.0002
FEV_1/FVC	53.8 (11.9)	48.9 (13.7)	56.0 (10.3)	0.006
Treatments				
No medication	19 (14)	3 (7)	16 (17)	–
LAMA	19 (14)	4 (9)	15 (16)	–
LABA	17 (12)	4 (9)	13 (14)	–
LAMA/LABA	58 (42)	21 (50)	37 (39)	–
ICS/LABA	11 (8)	7 (16)	4 (4)	–
ICS/LABA/LAMA	14 (10)	4 (9)	10 (10)	–
ICS dose, μg (FP equivalents dose)	507 (218)	494 (135)	515 (260)	0.25
Macrolide	12 (9)	5 (12)	7 (7)	0.63
Home oxygen therapy	11 (8)	5 (12)	6 (6)	0.47
Total number of moderate / severe exacerbations in previous year	39 / 25	39 / 25	–	–
Number of annual exacerbations in previous year / person-year	0.48 (0.88)	1.53 (0.94)	–	–
In previous 5 years / person-year*	0.39 (0.77)	1.08 (1.07)	0.08 (0.19)	<0.0001

Data are presented as n (% or range) or mean (standard deviation), unless otherwise stated.
P value was analyzed using Chi square test or Mann-Whitney U test between the groups.
*The observation period had a mean length of 45.4 months and maximum 60 months.
Abbreviations : COPD, chronic obstructive pulmonary disease ; FP, fluticasone propionate ; FVC, forced vital capacity ; %FVC, percentage of predicted FVC ; FEV_1, forced expiratory volume in 1 second ; $\%FEV_1$, percentage of predicted FEV_1 ; ICS, inhaled corticosteroid ; LABA, long-acting β_2 agonist ; LAMA, long-acting muscarinic antagonist

cant differences in these patients, compared with patients without an exacerbation, were greater age (77.3 ± 9.1 years vs 71.4 ± 7.7 years, p=0.03), poorer pulmonary function (such as $\%FEV_1$: 56.6 ± 18.3 vs 70.6 ± 19.4, p=0.006), lower PBE count (335 ± 81/μl vs 432 ± 133/μl, p=0.004), and greater average annual numbers in the previous 5 years of moderate-to-severe exacerbations (1.14 ± 1.22 vs 0.12 ± 0.22, p<0.0001) and of severe exacerbations (0.24 ± 0.33 vs 0 ± 0, p<0.0001). Of patients with eosinophilic COPD, 8 stopped being treated with inhaled corticosteroids within the previous 5 years ; this cessation of treatment was due to the absence of asthmatic features (n=4), pneumonia (n=1), and undetectable reasons (n=3). Of these 8 patients, 3 had COPD exacerbations after treatment had been stopped.

Of the 74 patients with noneosinophilic COPD, 21 (28%) had exacerbations (Table 3). Patients who had had an exacerbation, compared with patients who did not, had a significantly lower BMI (20.3 ± 2.9 vs 24.0 ± 3.9, p=0.0003), poorer pulmonary function (such as $\%FEV_1$: 57.8 ± 25.1 vs 71.8 ± 17.0, p=0.02), and greater average annual numbers in the previous 5 years of moderate-to-severe exacerbations and of severe exacerbations (1.02 ± 0.91 vs 0.04 ± 0.16, p<0.0001 ; 0.34 ± 0.43 vs 0 ± 0, p<0.0001). In the 13

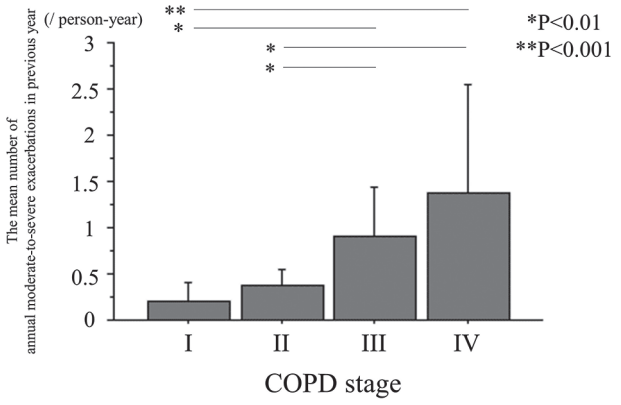

Fig. 1. Number of moderate-to-severe exacerbations of COPD
The mean number of annual exacerbations increased with the severity of COPD, and the number of stage III or IV exacerbations was significantly greater than that of stage I and II exacerbations. T bars represent the 95% confidence intervals.

patients with noneosinophilic COPD, the treatment with inhaled corticosteroids had been stopped within the previous 5 years ; treatment was stopped because of the absence of asthmatic features ($n=5$), repeated bronchitis/pneumonia ($n=4$), adverse effects ($n=2$), and undetectable reasons ($n=2$). Of these 13 patients, 5 had COPD exacerbations after the treatment with inhaled corticosteroids had been stopped.

From before to after exacerbation, the mean PBE count significantly decreased in patients with eosinophilic COPD (335 ± 81 to $183 \pm 212/\mu l$ [$n=20$], $p=0.01$) or with noneosinophilic COPD ($134 \pm 74/\mu l$ to $51 \pm 56/\mu l$ [$n=25$], $p<0.0001$, Wilcoxon signed-rank test). Although the length of the hospital stay was not correlated with the PBE count at the onset of the exacerbation, when the disease status was stable the length was correlated with the PBE count in patients with eosinophilic COPD (correlation coefficient= -0.61, $p=0.034$).

Risk factors for pneumonia

Of the episodes of exacerbation in the previous year, 33 were complicated by pneumonia in 28 patients, of whom 17 (61%) had no previous history of treatment with inhaled corticosteroids. During severe exacerbations, episodes of pneumonia occurred in 11 (92%) of 12 patients with eosinophilic COPD and in 12 (92%) of 13 patients with noneosinophilic COPD. Risk factors for pneumonia, identified with logistic regression analysis, were age (OR, 1.08 ; 95% CI, 1.00-1.16 ; $p=0.046$) and a history of exacerbation (OR, 7.5 ; 95% CI, 2.0-27.7 ; $p=0.003$) (Table 4). Identified as risk factors for pneumonia in patients with noneosinophilic COPD were the BMI (OR, 0.74 ; 95% CI, 0.56-0.98 ; $p=0.035$) and a history of exacerbations (OR, 20.4 ; 95% CI, 2.1-202 ; $p<0.001$), but a history of inhaled corticosteroid treatment was not associated with the incidence of pneumonia in these patients (OR, 0.41 ; 95% CI, 0.06-3.0 ; $p=0.38$; Table 4).

Table 2. Logistic regression analysis of risk factors for moderate-to-severe and severe exacerbation

	Moderate-to-severe exacerbation				Severe exacerbation			
	Univariate model		Multivariate model		Univariate model		Multivariate model	
	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value
Sex, male	0.67 (0.24-1.9)	0.45			0.94 (0.25-3.6)	0.93		
Age	1.07 (1.02-1.13)	0.008	1.04 (0.98-1.10)	0.19	1.13 (1.05-1.21)	0.0008	1.11 (1.02-1.21)	0.013
Body mass index	0.83 (0.74-0.92)	0.007	0.87 (0.77-0.97)	0.017	0.78 (0.68-0.91)	0.0012	0.84 (0.70-1.01)	0.06
COPD stage III / IV	4.5 (2.0-10.5)	0.0004	2.8 (1.1-7.0)	0.032	3.8 (1.4-9.9)	0.007	1.2 (0.34-3.9)	0.82
History of exacerbation, yes	−	>0.99			10.5 (3.2-34.6)	0.0001	8.8 (2.2-34.4)	0.002
PBE count ≥ 300 /μl	1.1 (0.56-2.4)	0.71			0.85 (0.34-2.2)	0.73		
History of ICS treatment†, yes	2.0 (0.94-4.2)	0.07	1.7 (0.71-3.9)	0.24	2.3 (0.92-5.8)	0.08	2.3 (0.72-7.1)	0.16
Dual bronchodilators‡, yes	1.4 (0.69-2.9)	0.35			1.8 (0.68-4.5)	0.24		

† Forty-six patients had history of ICS treatment.
‡ LAMA/LABA treatment
In multivariate model, we selected the parameters which p values were less than 0.20 in a univariate model.
Abbreviations : CI, confidence interval ; COPD, chronic obstructive pulmonary disease ; PBE, peripheral blood eosinophil ; ICS, inhaled corticosteroid ; LABA, long-acting β_2 agonists ; LAMA, long-acting muscarinic antagonists

Table 3. Characteristics of patients with eosinophilic or noneosinophilic chronic obstructive pulmonary disease

	Eosinophilic COPD (n=64)				Nonesosinophilic COPD (n=74)				p value between phenotypes
	All patients	Exacerbation (n=22)	No exacerbation (n=42)	p value between groups	All patients	Exacerbation (n=21)	No exacerbation (n=53)	p value between groups	
Male, n (%)	58 (89)	18 (82)	40 (95)	0.17	62 (84)	18 (86)	44 (83)	>0.99	0.35
Age, years	73.4 (8.6)	77.3 (9.1)	71.4 (7.7)	0.03	73.9 (7.0)	75.4 (5.5)	73.3 (7.5)	0.14	0.59
Body mass index, kg/m^2	23.5 (3.9)	22.5 (3.6)	24.0 (4.1)	0.13	23.0 (4.0)	20.3 (2.9)	24.0 (3.9)	0.0003	0.40
Smoking, former / current, n	54 / 11	19 / 3	34 / 8	0.73	65 / 9	17 / 4	48 / 5	0.26	0.55
Smoking index, pack-year	68 (43)	63 (29)	71 (49)	0.82	56 (29)	61 (29)	54 (28)	0.24	0.048
COPD stage I / II / III / IV, n	18 / 29 / 15 / 3	2 / 10 / 9 / 1	16 / 18 / 6 / 2	0.03	20 / 41/ 8 / 5	4 / 9 / 4 / 4	16 / 32 / 4 / 1	0.02	0.21
FVC, ml	3193 (862)	2732 (831)	3473 (739)	0.0006	3169 (831)	2896 (973)	3277 (751)	0.09	0.85
%FVC	95.3 (23.6)	89.0 (23.2)	99.4 (23.0)	0.05	98.0 (18.3)	91.2 (23.4)	100.6 (15.3)	0.14	0.73
FEV_1, ml	1722 (641)	1352 (585)	1931 (579)	0.0001	1744 (638)	1419 (684)	1872 (576)	0.01	0.74
%FEV_1	65.6 (20.0)	56.6 (18.3)	70.6 (19.4)	0.006	67.8 (20.5)	57.8 (25.1)	71.8 (17.0)	0.02	0.44
FEV_1/FVC	53.5 (11.5)	49.9 (13.2)	55.2 (10.2)	0.16	54.2 (12.3)	47.9 (14.5)	56.7 (10.4)	0.02	0.52
PBE, /μl in stable status	399 (125)	335 (81)	432 (133)	0.004	153 (75)	134 (74)	165 (72)	0.10	<0.0001
PBE, /μl during exacerbation in previous year	–	183 (212)[†]	–	–	–	51 (56)[‡]	–	–	0.04
Current ICS treatment, n (%)	21 (33)	8 (36)	13 (31)	0.87	4 (5)	3 (14)	1 (2)	0.07	<0.0001
Annual moderate-to-severe exacerbations in previous year, /person-year	0.48 (0.78)	1.41 (0.67)	–	–	0.47 (0.97)	1.67 (1.16)	–	–	0.50
Annual moderate-to-severe exacerbations in previous 5 years*, /person-year	0.47 (0.87)	1.14 (1.22)	0.12 (0.22)	<0.0001	0.32 (0.67)	1.02 (0.91)	0.04 (0.16)	<0.0001	0.05
Annual severe exacerbations in previous year, /person-year	0.20 (0.48)	0.59 (0.67)	–	–	0.19 (0.52)	0.67 (0.80)	–	–	0.72
Annual severe exacerbation in previous 5 years*, /person-year	0.08 (0.22)	0.24 (0.33)	0 (0)	<0.0001	0.09 (0.27)	0.34 (0.43)	0 (0)	<0.0001	0.78
Pneumonia in previous year, n	16 in 14 patients	–	–	–	17 in 14 patients	–	–	–	0.83
Length of hospital stay, days	–	14.0 (11.3) (n=11)	–	–	–	18.2 (14.7) (n= 14)	–	–	0.26
Systemic corticosteroid use while hospitalized, yes, n (%)	–	5 (45)	–	–	–	6 (55)	–	–	>0.99

Data are presented as n (%) or mean (standard deviation), unless otherwise stated.

P value was analyzed using chi square test, Fisher's exact test, or Mann-Whitney U test between the groups.

*The observation period was mean 45.4 months and maximum 60 months.

[†]Total numbers of exacerbations in patients with eosinophilic COPD were 19 moderate and 12 severe ; however, data were available for 20 cases.

[‡]Total numbers of exacerbations in patients with noneosinophilic COPD were 20 moderate and 13 severe ; however, data were available for 25 cases.

Abbreviations : COPD, chronic obstructive pulmonary disease ; FVC, forced vital capacity ; FEV_1, forced expiratory volume in 1 second ; %FEV_1, percentage of predicted FEV_1 ; PBE, peripheral blood eosinophil count ; ICS, inhaled corticosteroid

Table 4. Logistic regression analysis of risk factors for pneumonia

	All patients				Patients with eosinophilic COPD				Patients with noneosinophilic COPD			
	Univariate model		Multivariate model		Univariate model		Multivariate model		Univariate model		Multivariate model	
	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value
Sex, male	1.3 (0.35–4.9)	0.68			1.44 (0.16–13.5)	0.75			1.20 (0.23–6.2)	0.83		
Age	1.10 (1.04–1.17)	0.002	1.08 (1.00–1.16)	0.046	1.09 (1.01–1.18)	0.038	1.08 (0.98–1.18)	0.09	1.12 (1.02–1.24)	0.023	1.07 (0.94–1.22)	0.30
Body mass index	0.80 (0.70–0.92)	0.001	0.87 (0.75–1.00)	0.056	0.87 (0.73–1.02)	0.09	0.94 (0.77–1.14)	0.51	0.72 (0.58–0.90)	0.003	0.74 (0.56–0.98)	0.035
COPD stage III / IV	3.6 (1.5–8.8)	0.005	1.6 (0.5–4.5)	0.41	3.5 (1.02–12.3)	0.046	2.0 (0.51–8.2)	0.31	3.61 (0.96–13.6)	0.057	1.13 (0.19–6.6)	0.90
History of exacerbation, yes	9.9 (3.0–33)	0.0002	7.5 (2.0–27.7)	0.003	6.3 (1.2–32.5)	0.029	5.3 (0.89–31.7)	0.07	16.1 (2.7–96)	0.0023	20.4 (2.1–202)	<0.001
History of inhaled corticosteroid treatment[†], yes	1.4 (0.59–3.3)	0.46			0.81 (0.25–2.7)	0.73			2.48 (0.69–8.8)	0.16	0.41 (0.06–3.0)	0.38
Dual bronchodilators[‡], yes	1.5 (0.7–3.6)	0.31			1.3 (0.4–4.4)	0.64			1.80 (0.54–6.0)	0.34		

[†]Forty-six patients had a history of inhaled corticosteroid treatment.
[‡]Treatment with long-acting β_2 agonists and long-acting muscarinic antagonists
In multivariate model, we selected the variables that had p values less than 0.20 in a univariate model.
Abbreviations : CI, confidence interval ; COPD, chronic obstructive pulmonary disease

DISCUSSION

The present study has found that the mean number of moderate-to-severe exacerbations in patients with COPD was approximately 0.4 to 0.5/person-year, which was comparable to the numbers in previous studies in Japanese patients but fewer than in studies of European patients[12,13]. For the exacerbation rate being lower in Japan than in other countries, several reasons have been suggested and include behavioral characteristics, access to medical care, environmental factors, and strict COPD diagnostic criteria[14]. Consistent with previous studies, the present study has shown that patients with exacerbations had a significantly greater age, lower BMI, poorer pulmonary function, and previous exacerbations. Although the present study was retrospective and involved only a single hospital, we believe that the patients reflect the general COPD population in Japan.

As a clinical biomarker of the characteristics of COPD, the PBE count has recently attracted attention[15,16]. An elevated PBE count has been reported to be associated with not only a higher frequency of COPD exacerbations but also shorter hospital stays and lower mortality rates[11,17-20]. Although previous randomized controlled trials and clinical studies have demonstrated the usefulness of a PBE count≥150/μl[6,18,21], the present study used a PBE count≥300/μl on the basis of the GOLD guidelines 2020[1] and other reports[11,20-24]. Although a previous study of 2 worldwide COPD cohorts has demonstrated that 43% to 60% of patients had a persistent or intermittent PBE count≥300/μl based on the 3 measurements at different timepoints[20], several studies of Japanese patients with COPD have demonstrated that such a PBE count was present in approximately 20% of patients[25,26]. In disagreement with previous Japanese studies, the present study found that the prevalence of eosinophilic COPD was 46% in all patients. In the present study, we defined the eosinophilia phenotype on the basis of a single blood examination during a time of stable disease status. We also reclassified the phenotypes of eosinophilia by using 3 measurements at different timepoints: 25% were persistent, and 23% were intermittent eosinophilia, which was similar to previous reports[20,25,26]. Furthermore, clinical characteristics, other than the PBE count, did not differ significantly among patients with persistent, intermittent, and noneosinophilic COPD phenotypes at baseline (data not shown). Therefore, we believe that our definition of the eosinophilic COPD phenotype is comparable to those from previous studies.

Previous studies have found that therapy including inhaled corticosteroids can reduce the exacerbation rate and that systemic corticosteroid therapy is useful for severe exacerbations, especially in patients with eosinophilic COPD[27,28]. Because the present study found no significant difference in the number of annual exacerbations between patients with eosinophilic COPD and patients with noneosinophilic COPD, we speculate that the explanation is the more frequent use of inhaled corticosteroids for patients with eosinophilic COPD. The PBE count during exacerbation has been reported to be elevated, based on a cutoff value of 150/μl or 2%, in 20% to 40% of patients with COPD[4,29,30]. Consistent with this observation, of the 58 episodes of moderate-to-severe exacerbations in the present study, 45 were documented with blood tests, and 13 (29%) were eosinophilic exacerbations. However, systemic corticosteroid therapy was often performed regardless of the exacerbation's phenotype. Hence, in future studies, more patients should be included and the appropriate systemic corticosteroid treatment strategy based on the exacerbation phenotype should be examined.

The length of hospital stay has been reported to be inversely correlated with the PBE count at the onset of COPD exacerbation[17,19]. However, in the present study the PBE count, while the disease status was stable but not at the onset of an exacerbation, was inversely correlated with the length of hospital stay of patients with eosinophilic COPD. A previous study showed that an increased PBE count when the disease status was stable might be associated with a higher frequency of exacerbations, mainly due to eosinophilic inflammation[31]. Although the PBE count at the onset of exacerbation was decreased in patients with either eosinophilic COPD or noneosinophilic COPD in the present study, the absolute eosinophil counts were significantly higher in patients with eosinophilic COPD (183±212/μl) than in patients with noneosinophilic COPD (51±56/μl, $p=0.04$, Table 3). Accordingly, an increased PBE count while the disease status is stable and a relatively high eosinophil count with a concomitantly increased neutrophil count at the onset of exacerbation likely indicate the coexistence of both eosinophilic and neutrophilic inflammation during an exacerbation in patients with eosinophilic COPD[4]. The coexistence of several different causes of COPD exac-

erbation is not surprising, and bacterial infection was most involved in COPD exacerbations in the present study, resulting in a decreased PBE count at the onset of exacerbations in patients with either eosinophilic or noneosinophilic COPD. Hence, we speculate that PBE, while the disease status is stable, more properly reflects the coexistence of eosinophilic inflammation and the response to corticosteroid treatment in the context of COPD exacerbations caused by bacterial infections in patients with eosinophilic COPD.

The present study demonstrated, with multivariate logistic regression analysis, that the risk factors for moderate-to-severe exacerbations were BMI and COPD stage, a finding that is consistent with those of previous studies[12,20]. However, the PBE count and inhaled corticosteroids use were not associated with moderate-to-severe exacerbations. Although a meta-analysis has found that patients with COPD but without eosinophilia have more episodes of pneumonia than do patients with eosinophilia among patients receiving inhaled corticosteroid treatment[32], multivariate logistic regression analysis in the present study found that inhaled corticosteroid use was not associated with the prevalence of pneumonia in all patients or in patients with noneosinophilic COPD (Table 4). In general, inhaled corticosteroid therapy for patients with COPD has been reported to increase the risk of pneumonia, particularly in patients with greater age, lower BMI, severely limited airflow, and a low PBE count[24]. On the other hand, the risk of pneumonia might depend on the type of inhaled corticosteroid[24,33], and inhaled corticosteroid therapy for patients with COPD in Japan might not significantly increase the risk of pneumonia[34], owing to ethnic differences[13]. We speculate that the lack of association of inhaled corticosteroid treatment with pneumonia in the present study has several explanations. First, the mean age of patients (74 years) in the present study was greater than in randomized controlled trials (65 years)[35,36]. Age is a strong risk factor for pneumonia and might have decreased the effect of inhaled corticosteroids. A second explanation is that the dose of inhaled corticosteroids was lower in the present study than in previous studies and can be attributed to the difference in the approved dosage for COPD in Japan (1,000 μg vs. 500 μg of fluticasone propionate equivalent dose). These facts suggest that in patients with COPD and an eosinophilic phenotype, inhaled corticosteroid use reduces the rate of moderate-to-severe exacerbations without increasing the risk of pneumonia.

Despite its findings, the present study has several limitations. First, although we believe a benefit of this study is the use of real-world data from Japan, this single-center, retrospective study enrolled only 138 patients ; therefore, future studies should include more patients. A second limitation is that we could not adjust for systemic comorbidities. We focused on examining the risk of COPD exacerbation but not on the risk of death from exacerbations, and adjustment for comorbidities may be unnecessary. A third limitation of the present study is that because single inhaler triple therapy has only recently become available in Japan, it has been administered to few patients. The difference between single-device and multiple-device inhalers is unclear ; however, single-inhaler triple therapy might improve adherence. In the future, prospective studies with a larger cohort are needed to clarify the relationship between inhaled corticosteroid use and the risk of exacerbation in Japanese patients and to evaluate the effects of systemic comorbidities.

Conclusions

Consistent with previous studies, the present study identified greater age, lower BMI, severe COPD, and a history of exacerbation as risk factors for moderate-to-severe exacerbations in Japanese patients with COPD. Although we did not observe, with multivariate logistic regression analysis, an association between the use of inhaled corticosteroids and the risk of exacerbation, treatment with inhaled corticosteroids might decrease the risk of exacerbation in patients with COPD and eosinophilia.

Authors' contributions

TN designed the study and performed the statistical analysis, and TN wrote the manuscript. TN, JA, YM, KO, JW, NT, HM, YF, DT, HU, MH, SI, HW, and SM contributed to data collection. TN, JA, HH, and KK interpreted the results. All authors read and approved the final manuscript.

Authors have no conflicts of interest.

REFERENCES

1. Global Initiative for Chronic Obstructive Lung Disease. 2020 GOLD Report : Global strategy for the diagnosis, management and prevention of chronic obstructive lung disease. Global Initiative for Chronic Obstructive Lung Disease, 2020. https://goldcopd.org/gold-reports/. [accessed 2021-12-20]
2. Fukuchi Y, Nishimura M, Ichinose M, Adachi M, Nagai A, Kuriyama T, et al. COPD in Japan : the Nippon COPD Epidemiology study. Respirology. 2004 ; 9 : 458-65.
3. Soler-Cataluña JJ, Martínez-García MÁ, Román Sánchez P, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. Thorax. 2005 ; 60 : 925-31.
4. Bafadhel M, Mckenna S, Terry S, Mistry V, Reid C, Haldar P, et al. Acute exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2011 ; 184 : 662-71.
5. The Japanese Respiratory Society. The JRS Guidelines for the management of chronic obstructive pulmonary disease (in Japanese). 5th ed. Tokyo : The Japanese Respiratory Society ; 2018.
6. Lipson DA, Barnhart F, Brealey N, Brooks J, Criner GJ, Day NC, et al. Once-daily single-inhaler triple versus dual therapy in patients with COPD. N Engl J Med. 2018 ; 378 : 1671-80.
7. Ferguson GT, Rabe KF, Martinez FJ, Fabbri LM, Wang C, Ichinose M, et al. Triple therapy with budesonide/glycopyrrolate/formoterol fumarate with co-suspension delivery technology versus dual therapies in chronic obstructive pulmonary disease (KRONOS) : a double-blind, parallel-group, multicentre, phase 3 randomised controlled trial. Lancet Respir Med. 2018 ; 6 : 747-58.
8. Yanagisawa S, Ichinose M. Definition and diagnosis of asthma-COPD overlap (ACO). Allergol Int. 2018 ; 67 : 172-8.
9. Global Initiative for Chronic Obstructive Lung Disease. 2017 GOLD Report : Global strategy for the diagnosis, management and prevention of chronic obstructive lung disease. Global Initiative for Chronic Obstructive Lung Disease, 2017. https://goldcopd.org/gold-reports/. [accessed 2017-4-29]
10. Yun JH, Lamb A, Chase R, Singh D, Parker MM, Saferali A, et al. Blood eosinophil count thresholds and exacerbations in patients with chronic obstructive pulmonary disease. J Allergy Clin Immunol. 2018 ; 141 : 2037-47.e10.
11. Zeiger RS, Tran TN, Butler RK, Schatz M, Li Q, Khatry DB, et al. Relationship of blood eosinophil count to exacerbations in chronic obstructive pulmonary disease. J Allergy Clin Immunol Pract. 2018 ; 6 : 944-54.e5.
12. Suzuki M, Makita H, Ito YM, Nagai K, Konno S, Nishimura M. Clinical features and determinants of COPD exacerbation in the Hokkaido COPD cohort study. Eur Respir J. 2014 ; 43 : 1289-97.
13. Ichinose M, Nishimura M, Akimoto M, Kurotori Y, Zhao Y, de la Hoz A, et al. Tiotropium/olodaterol versus tiotropium in Japanese patients with COPD : results from the DYNAGITO study. Int J Chron Obstruct Pulmon Dis. 2018 ; 13 : 2147-56.
14. Ishii T, Nishimura M, Akimoto A, James MH, Jones P. Understanding low COPD exacerbation rates in Japan : A review and comparison with other countries. Int J COPD. 2018 ; 13 : 3459-71.
15. Brusselle G, Pavord ID, Landis S, Pascoe S, Lettis S, Morjaria N, et al. Blood eosinophil levels as a biomarker in COPD. Respir Med. 2018 ; 138 : 21-31.
16. Vedel-Krogh S, Nielsen SF, Lange P, Vestbo J, Nordestgaard BG. Blood eosinophils and exacerbations in chronic obstructive. Am J Respir Crit Care Med. 2016 ; 193 : 965-74.
17. Bafadhel M, Greening NJ, Harvey-Dunstan TC, Williams JEA, Morgan MD, Brightling CE, et al. Blood eosinophils and outcomes in severe hospitalized exacerbations of COPD. Chest. 2016 ; 150 : 320-8.
18. MacDonald MI, Osadnik CR, Bulfin L, Hamza K, Leong P, Wong A, et al. Low and high blood eosinophil counts as biomarkers in hospitalized acute exacerbations of COPD. Chest. 2019 ; 156 : 92-100.
19. Ko FWS, Chan KP, Ngai J, Ng SS, Yip WH, IP A, et al. Blood eosinophil count as a predictor of hospital length of stay in COPD exacerbations. Respirology. 2020 ; 25 : 259-66.
20. Casanova C, Celli BR, de-Torres JP, Martinez-Gonzalez C, Cosio BG, Pinto-Plata V, et al. Prevalence of persistent blood eosinophilia : relation to outcomes in patients with COPD. Eur Respir J. 2017 ; 50 : 1701162.
21. Roche N, Chapman KR, Vogelmeier CF, Herth FJF, Thach C, Fogel R, et al. Blood eosinophils and response to maintenance chronic obstructive pulmonary disease treatment data from the FLAME Trial. Am J Respir Crit Care Med. 2017 ; 195 : 1189-97.
22. Watz H, Tetzlaff K, Wouters EFM, Kirsten A, Magnussen H, Rodriguez-Roisin R, et al. Blood eosinophil count and exacerbations in severe chronic obstructive pulmonary disease after withdrawal of inhaled corticosteroids : A post-hoc analysis of the WISDOM trial. Lancet Respir Med. 2016 ; 4 : 390-8.
23. Calverley PMA, Tetzlaff K, Vogelmeier C, Fabbri LM, Magnussen H, Wouters EFM, et al. Eosinophilia, frequent exacerbations, and steroid response in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2017 ; 196 : 1219-21.
24. Agusti A, Fabbri LM, Singh D, Vestbo J, Celli B, Franssen FME, et al. Inhaled corticosteroids in COPD : Friend or foe? Eur Respir J. 2018 ; 52 : 1801219.
25. Barnes N, Ishii T, Hizawa N, Midwinter D, James M, Hilton E, et al. The distribution of blood eosinophil levels in a Japanese COPD clinical trial database and in the rest of the world. Int J Chron Obstruct Pulmon Dis. 2018 ; 13 : 433-40.
26. Suzuki M, Makita H, Konno S, Shimizu k, Kimura H, Kimura H, et al. Asthma-like features and clinical course of chronic obstructive pulmonary disease. an analysis from the Hokkaido COPD Cohort Study. Am J Respir Crit Care Med. 2016 ; 194 : 1358-65.
27. Serafino-Agrusa L, Scichilone N, Spatafora M, Battaglia S. Blood eosinophils and treatment response in hospitalized exacerbations of chronic obstructive pulmonary disease : A case-control study. Pulm Pharmacol Ther. 2016 ; 37 : 89-94.
28. Sivapalan P, Lapperre TS, Janner J, Laub RR, Moberg M, Bech

CS, et al. Eosinophil-guided corticosteroid therapy in patients admitted to hospital with COPD exacerbation (CORTICOCOP) : a multicentre, randomised, controlled, open-label, non-inferiority trial. Lancet Respir Med. 2019 ; 7 : 699-709.
29. Singh D, Kolsum U, Brightling CE, Locantore N, Agusti A, Tal-Singer R. Eosinophilic inflammation in COPD : Prevalence and clinical characteristics. Eur Respir J. 2014 ; 44 : 1697-700.
30. Brightling CE, Monteiro W, Ward R, Parker D, Morgan MDL, Wardlaw AJ, et al. Sputum eosinophilia and short-term response to prednisolone in chronic obstructive pulmonary disease : A randomised controlled trial. Lancet. 2000 ; 356(9240) : 1480-5.
31. Bafadhel M, McKenna S, Terry S, Mistry V, Pancholi M, Venge P, et al. Blood eosinophils to direct corticosteroid treatment of exacerbations of chronic obstructive pulmonary disease : A randomized placebo-controlled trial. Am J Respir Crit Care Med. 2012 ; 186 : 48-55.
32. Pavord ID, Lettis S, Anzueto A, Barnes N. Blood eosinophil count and pneumonia risk in patients with chronic obstructive pulmonary disease : a patient-level meta-analysis. Lancet Respir Med. 2016 ; 4 : 731-41.
33. Finney L, Berry M, Singanayagam A, Elkin SL, Johnston SL, Mallia P. Inhaled corticosteroids and pneumonia in chronic obstructive pulmonary disease. Lancet Respir Med. 2014 ; 2 : 919-32.
34. Hirano R, Fujita M, Matsumoto T, On R, Watanabe K. Inhaled corticosteroids might not increase the risk of pneumonia in patients with chronic obstructive pulmonary disease in Japan. Int J Chron Obstruct Pulmon Dis. 2018 ; 13 : 3503-9.
35. Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med. 2007 ; 356 : 775-89.
36. Wedzicha JA, Calverley PMA, Seemungal TA, Hagan G, Ansari Z, Stockley RA. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. Am J Respir Crit Care Med. 2008 ; 177 : 19-26.